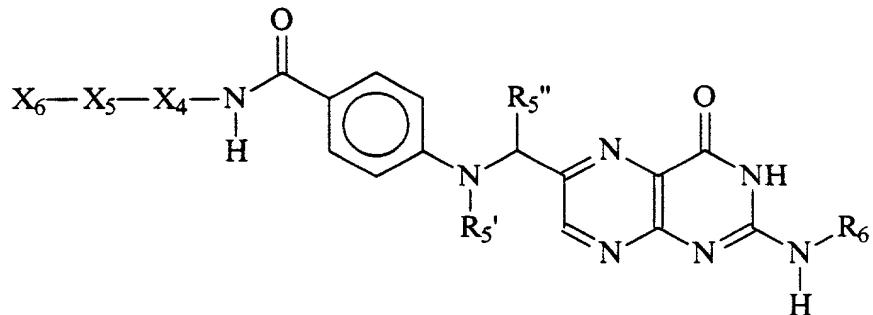


What is claimed is:

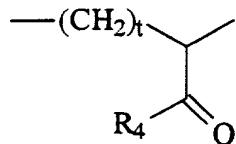
1. A compound of the formula:



wherein:

X_4 is $-\text{CH}(X_4\text{.})$ or a group of formula:

5



$X_4\text{.}$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X_5 is $-\text{N}(X_6\text{.})\text{C(O)-}$, $-\text{C(O)NH-}$, $-\text{NHC(O)-}$, $-\text{OC(O)NH-}$,
 10 $-\text{C(S)NH-}$, $-\text{SC(S)NH-}$, $-\text{SC(O)NH-}$, $-\text{OC(S)NH-}$, $-\text{C(O)O-}$,
 $-\text{C(O)(CH}_2\text{)}_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and $X_6\text{.}$ is, independently, hydrogen or a hydrocarbyl group selected from $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{20}$ alkynyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_6\text{-C}_{14}$ aralkyl, $\text{C}_3\text{-C}_{14}$ cycloalkyl, $\text{C}_5\text{-C}_{14}$ fused cycloalkyl, $\text{C}_4\text{-C}_{14}$ heterocycle, $\text{C}_4\text{-C}_{14}$ heterocyclalkyl, $\text{C}_4\text{-C}_{14}$ heteroaryl and $\text{C}_4\text{-C}_{14}$ heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, 20 acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,

alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen;

R₄ is a hydroxyl group or a protected hydroxyl group;

5 R₅ is hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₂₀ alkynyl, C₆-C₁₄ aryl or an amino-protecting group

R₅.. is hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₂₀ alkynyl, C₆-C₁₄ aryl, C₆-C₁₄ aralkyl, C₃-C₁₄ cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

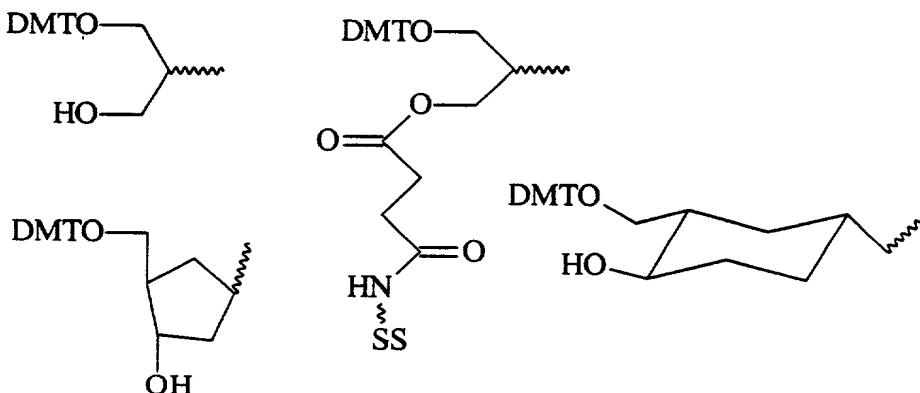
10 R₆ is hydrogen or an amino protecting group; and t is 1 or 2.

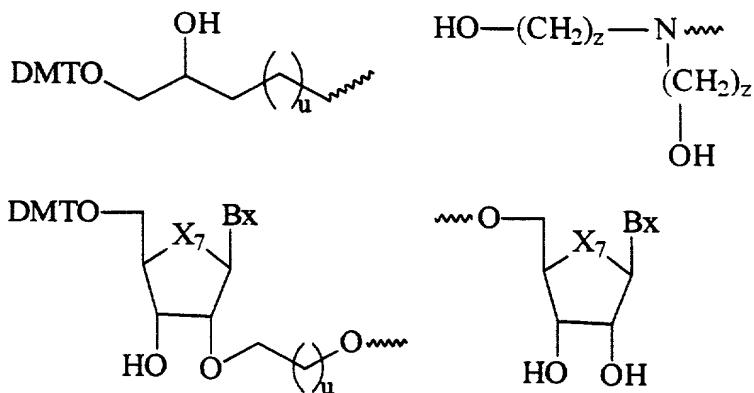
2. The compound of claim 1 wherein said amino acid is amino caproic acid.

3. The compound of claim 1 connected to an 15 oligonucleotide by a disulfide group.

4. The compound of claim 1 wherein said X₄ is the side chain of glutamic acid.

5. The compound of claim 1 wherein said X₆ has one of the formulas:





wherein:

SS is a solid support;

X₇ is O or CH₂;

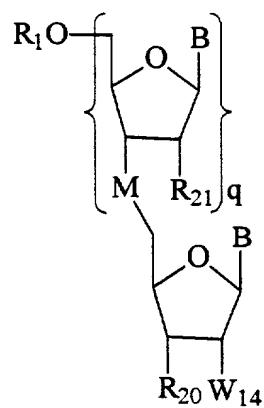
Bx is a nucleobase, C₄-C₁₄ heterocyclyl or hydrogen;

5 z is an integer from 1 to 50; and

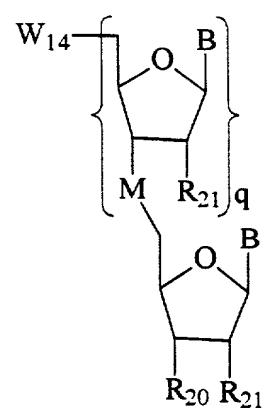
u is an integer from 2 to 5.

6. The compound of claim 1 wherein said X₆ is attached to a solid support.

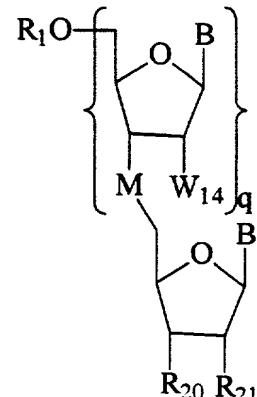
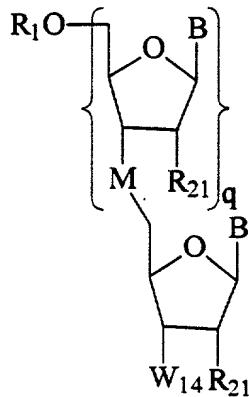
7. A compound having formula XVIA, XVIB, XVIC or XVID:



XVIA

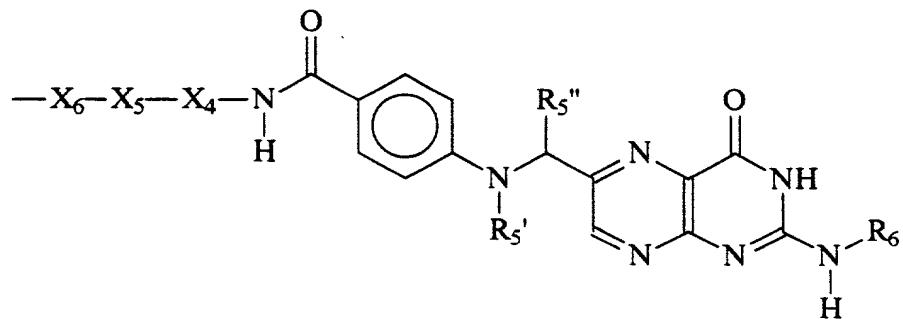


XVIC



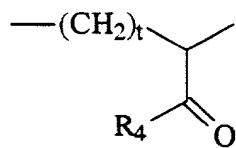
wherein:

W_{14} has the formula:



wherein:

X_4 is $-\text{CH}(X_4')$ or a group of formula:



X_4 is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

5 t is 1 or 2;

X_5 is $-N(X_6)C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$,

$-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$,

$-C(O)(CH_2)_n-$ or a bond;

10 n is an integer from 1 to 50;

10 each X_6 and X_6' is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl;

15 wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, 20 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and X_6' is not a bond;

15 R_1 is hydrogen or a hydroxyl protecting group;

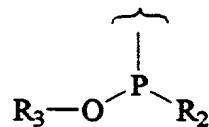
25 R_4 is a hydroxyl group or a protected hydroxyl group;

25 each R_5 and R_{40} is, independently, hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

30 R_5 is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, 30 aminoalkyl or hydroxymethyl;

30 R_6 is hydrogen or an amino protecting group;

R_{20} is hydrogen or a group of formula:



R_2 is $-\text{N}(\text{R}_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and 5 having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

R_3 is a phosphorus protecting group;

10 R_{21} is hydrogen, hydroxyl, fluoro or a group of formula $Z-\text{R}_{22}-(\text{R}_{23})_v$;

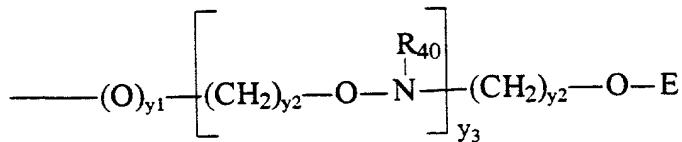
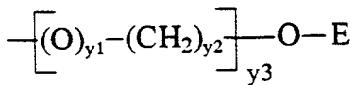
Z is O, S, NH or $N-\text{R}_{22}-(\text{R}_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

15 R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, 20 disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

25 or R_{21} has one of the formulas:

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wherein:

y₁ is 0 or 1;

each y₂ is, independently, 0 to 10;

5 y₃ is 1 to 10;

E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with 10 the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

B is a nucleobase;

M is an optionally protected internucleoside linkage;

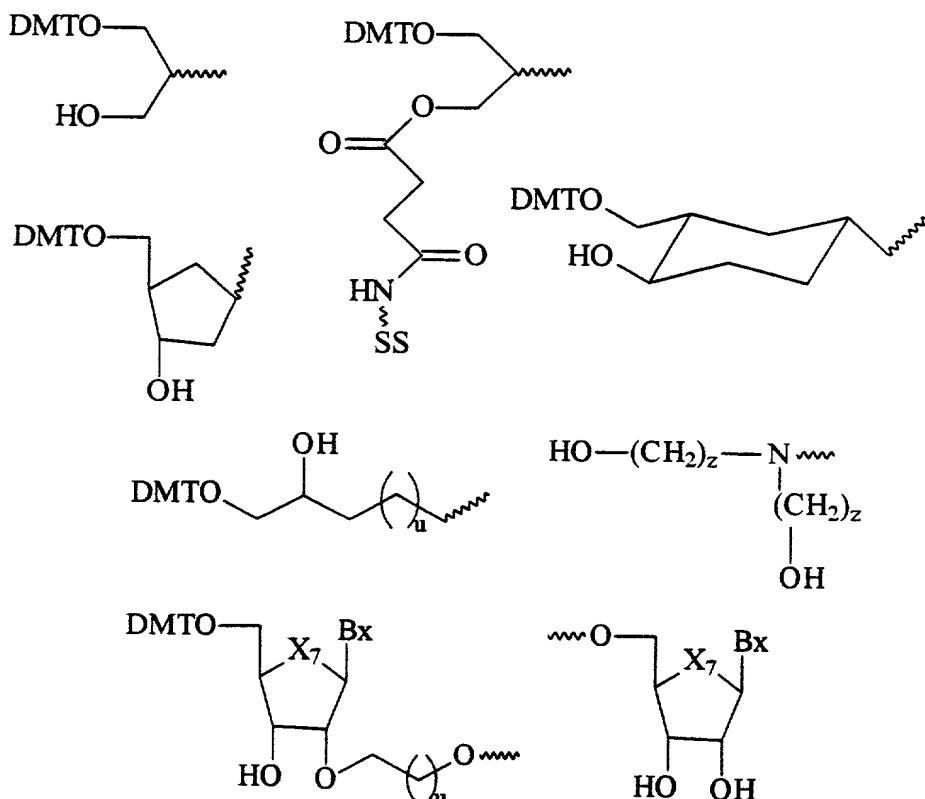
15 q is from zero to about 50; and

v is from zero to about 10.

8. The compound of claim 7 wherein said amino acid is amino caproic acid.

9. The compound of claim 7 wherein said X₄ is the side 20 chain of glutamic acid.

10. The compound of claim 7 wherein said X₆ has one of the formulas:



wherein

SS is a solid support;

5 X₇ is O or CH₂;

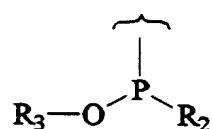
Bx is a nucleobase, C₄-C₁₄ heterocyclyl or hydrogen;

z is an integer from 1 to 50; and

u is an integer from 2 to 5.

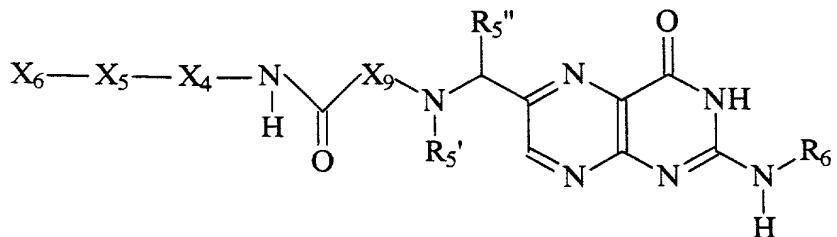
11. The compound of claim 7 wherein said R₁ is
10 dimethoxytrityl.

12. The compound of claim 7 wherein said R₂₀ is a group
of formula:



wherein R_2 is diisopropylamino and R_3 is β -cyanoethyl.

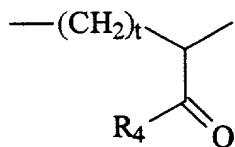
13. A compound of the formula:



wherein:

X_4 is $-CH(X_4')$ or a group of formula:

5



X_4' is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

10 X_5 is $-N(X_6')C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$,
 $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$,
 $-C(O)(CH_2)_n-$ or a bond;

15 n is an integer from 1 to 50;

each X_6 , X_6' , and X_9 is, independently, a bond, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclalkyl, wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that each of X_6 and X_6' is not a bond and X_6 is not hydrogen;

R_4 is a hydroxyl group or a protected hydroxyl group;

R_5 is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

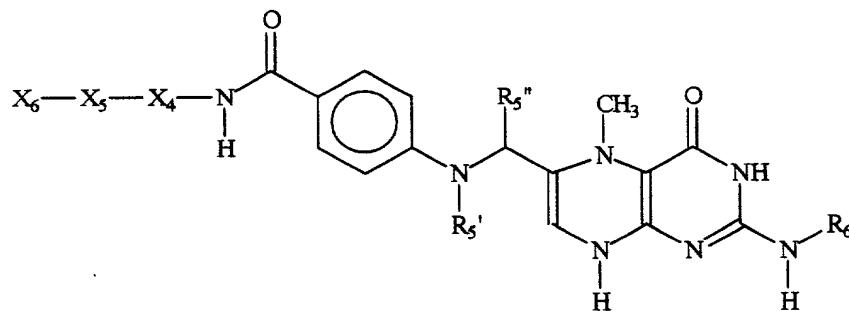
R_5' is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group; and
10 t is 1 or 2.

14. The compound of claim 13 wherein said amino acid is aminocaproic acid

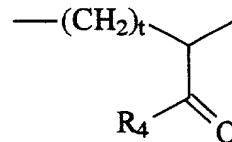
15. The compound of claim 13 connected to an oligonucleotide by a disulfide group.

15 16. A compound of the formula:



wherein:

X_4 is $-CH(X_4')$ or a group of formula:



X_4' is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X_5 is $-N(X_6)C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-OC(O)NH-$,
 $-C(S)NH-$, $-SC(S)NH-$, $-SC(O)NH-$, $-OC(S)NH-$, $-C(O)O-$,
 $-C(O)(CH_2)_n-$ or a bond;

n is an integer from 1 to 50;

5 each X_6 and X_6' is, independently, hydrogen or a hydrocarbyl group selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, C_5-C_{14} fused cycloalkyl, C_4-C_{14} heterocycle, C_4-C_{14} heterocyclalkyl, C_4-C_{14} heteroaryl and C_4-C_{14} heteroarylalkyl;
10 wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT,
15 alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen;

R_4 is a hydroxyl group or a protected hydroxyl group;

20 R_5 is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

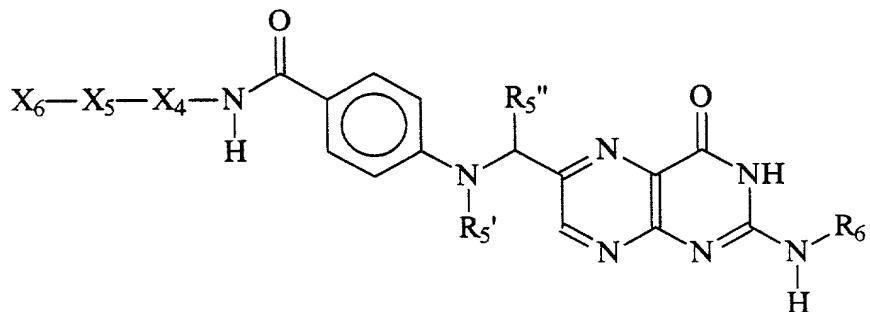
25 R_6 is hydrogen or an amino protecting group; and

t is 1 or 2.

17. The compound of claim 16 wherein said amino acid is aminocaproic acid.

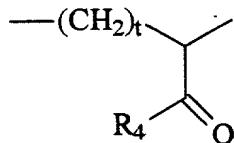
18. The compound of claim 16 connected to an oligonucleotide by a disulfide group.

30 19. A method of preparing compounds of formula XVII:



XVII

wherein:

X₄ is -CH(X₄.) or a group of formula:

X₄ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

X₅ is -N(X₆.)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-,
 10 -C(S)NH-, -SC(S)NH-, -SC(O)NH-, -OC(S)NH-, -C(O)O-,
 -C(O)(CH₂)_n- or a bond;
 n is an integer from 1 to 50;
 each X₆ and X₆. is, independently, hydrogen or a hydrocarbyl group selected from C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
 15 C₂-C₂₀ alkynyl, C₆-C₁₄ aryl, C₆-C₁₄ aralkyl, C₃-C₁₄ cycloalkyl, C₅-C₁₄ fused cycloalkyl, C₄-C₁₄ heterocycle, C₄-C₁₄ heterocyclalkyl, C₄-C₁₄ heteroaryl and C₄-C₁₄ heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxycarbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen;

R_4 is a hydroxyl group or a protected hydroxyl group;

R_5 , is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20}

5 alkynyl, C_6-C_{14} aryl or an amino-protecting group

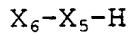
R_5 , is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group; and

10 t is 1 or 2;

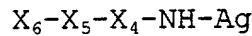
comprising the steps of:

(a) providing a hydroxy compound of formula:



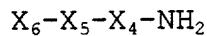
(b) protecting said hydroxyl groups of X_6 with protecting 15 groups to form a protected hydroxy compound;

(c) reacting said protected hydroxy compound with an amino-protected amino acid to form a covalently linked hydroxy compound of formula:



20 wherein Ag is an amino protecting group;

(d) cleaving the amino-protecting group of said covalently linked hydroxy compound to form a hydroxy compound bearing a deprotected amino group and having formula:



25 (e) reacting said amino group with a folate moiety; and

(f) cleaving the protecting groups on said hydroxyl groups of step (b) to form a compound of formula XVII.

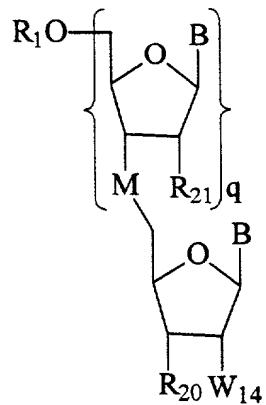
20. The method of claim 19 further comprising the steps of:

30 (g) protecting one of said hydroxyl groups of X_6 with a dimethoxytrityl group; and

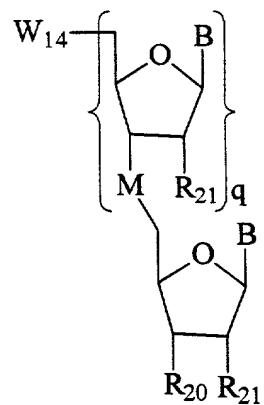
(h) phosphitylating the other of said hydroxyl groups of

X₆.

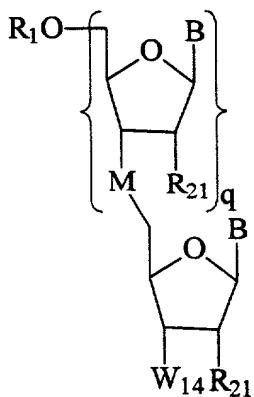
21. A compound having formula XVIA, XVIB, XVIC or XVID:



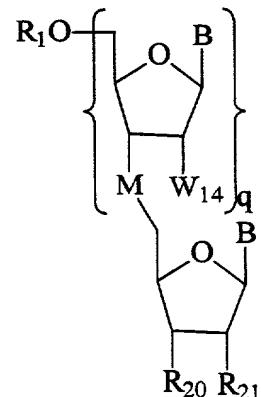
XVIA



XVIC



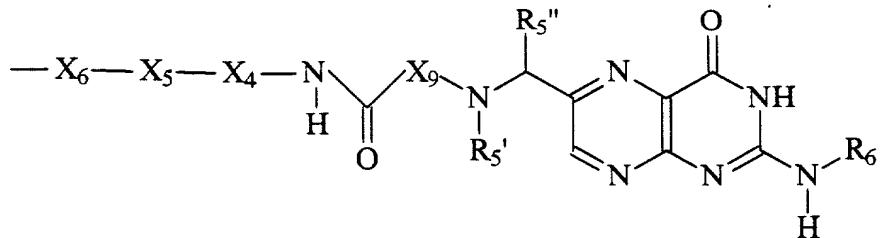
XVIB



XVID

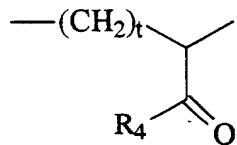
5 wherein:

W₁₄ has the formula:



wherein:

X_4 is $-\text{CH}(X_4\cdot)$ or a group of formula:



$X_4\cdot$ is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

5 t is 1 or 2;

X_5 is $-\text{N}(X_6\cdot)\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{NHC}(\text{O})-$, $-\text{OC}(\text{O})\text{NH}-$,
 $-\text{C}(\text{S})\text{NH}-$, $-\text{SC}(\text{S})\text{NH}-$, $-\text{SC}(\text{O})\text{NH}-$, $-\text{OC}(\text{S})\text{NH}-$, $-\text{C}(\text{O})\text{O}-$,

10 $-\text{C}(\text{O})(\text{CH}_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 , $X_6\cdot$ and X_5 is, independently, a bond, hydrogen or a hydrocarbyl group selected from $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{20}$ alkynyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_6\text{-C}_{14}$ aralkyl, $\text{C}_3\text{-C}_{14}$ cycloalkyl,

15 $\text{C}_5\text{-C}_{14}$ fused cycloalkyl, $\text{C}_4\text{-C}_{14}$ heterocycle, $\text{C}_4\text{-C}_{14}$ heterocyclalkyl, $\text{C}_4\text{-C}_{14}$ heteroaryl and $\text{C}_4\text{-C}_{14}$ heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate,

sulfonamide, thiol, and thioalkoxy; provided that each X_6 and X_7 is not hydrogen and X_6 is not a bond;

R_1 is hydrogen or a hydroxyl protecting group;

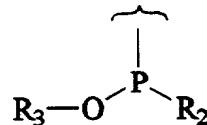
R_4 is a hydroxyl group or a protected hydroxyl group;

5 each R_5 , and R_{40} is, independently, hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl or an amino-protecting group

10 R_{50} is hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{20} alkynyl, C_6-C_{14} aryl, C_6-C_{14} aralkyl, C_3-C_{14} cycloalkyl, formyl, aminoalkyl or hydroxymethyl;

R_6 is hydrogen or an amino protecting group;

R_{20} is hydrogen or a group of formula:



15 R_2 is $-\text{N}(\text{R}_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

20 R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

20 R_3 is a phosphorus protecting group;

20 R_{21} is hydrogen, hydroxyl, fluoro or a group of formula $Z-\text{R}_{22}-(\text{R}_{23})_v$;

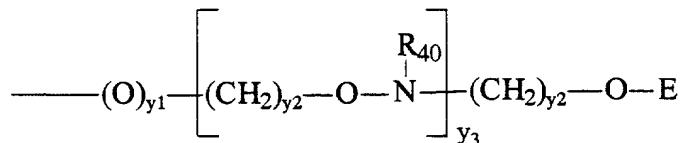
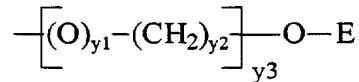
20 Z is O, S, NH or $N-\text{R}_{22}-(\text{R}_{23})_v$;

20 R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

25 R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, 30 hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

5 or R_{21} has one of the formulas:



wherein:

y_1 is 0 or 1;

each y_2 is, independently, 0 to 10;

10 y_3 is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;

each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with 15 the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

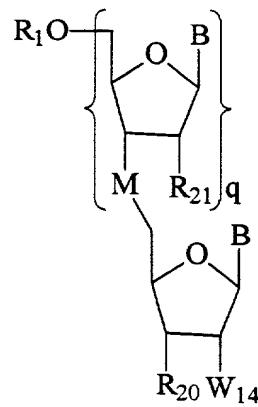
B is a nucleobase;

M is an optionally protected internucleoside linkage;

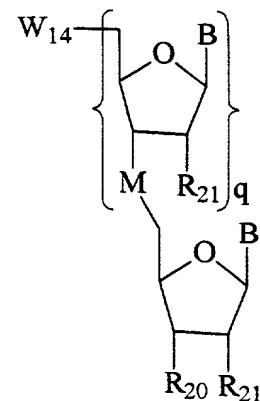
20 q is from zero to about 50; and

v is from zero to about 10.

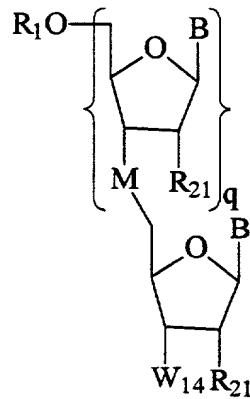
22. A compound having formula XVIA, XVIB, XVIC or XVID:



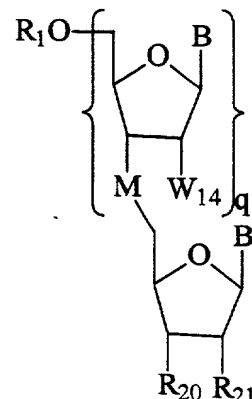
XVIA



XVIC



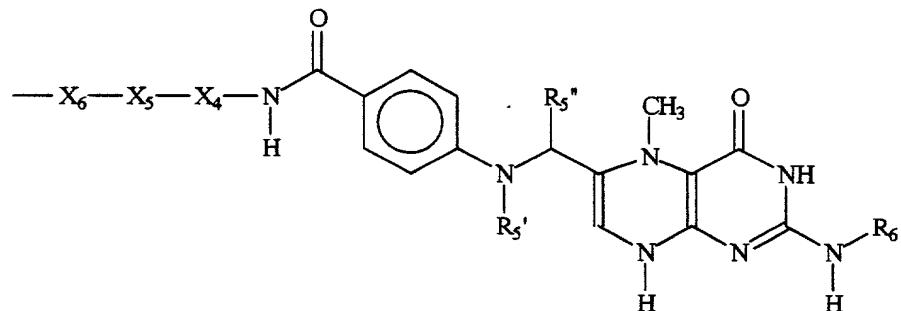
XVIB



XVID

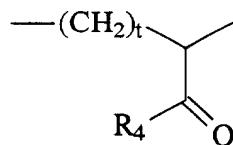
wherein:

W_{14} has the formula:



wherein:

X_4 is $-\text{CH}(X_4)$ or a group of formula:



X_4 is the side chain of a naturally-occurring or non-naturally-occurring amino acid, or a protected side chain of a naturally-occurring or non-naturally-occurring amino acid;

t is 1 or 2;

X_5 is $-\text{N}(X_6)\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{NHC}(\text{O})-$, $-\text{OC}(\text{O})\text{NH}-$,
 $-\text{C}(\text{S})\text{NH}-$, $-\text{SC}(\text{S})\text{NH}-$, $-\text{SC}(\text{O})\text{NH}-$, $-\text{OC}(\text{S})\text{NH}-$, $-\text{C}(\text{O})\text{O}-$,
 $-\text{C}(\text{O})(\text{CH}_2)_n-$ or a bond;

n is an integer from 1 to 50;

each X_6 and X_6' is, independently, a bond, hydrogen or a hydrocarbyl group selected from $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{20}$ alkynyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_6\text{-C}_{14}$ aralkyl, $\text{C}_3\text{-C}_{14}$ cycloalkyl, $\text{C}_5\text{-C}_{14}$ fused cycloalkyl, $\text{C}_4\text{-C}_{14}$ heterocycle, $\text{C}_4\text{-C}_{14}$ heterocyclalkyl, $\text{C}_4\text{-C}_{14}$ heteroaryl and $\text{C}_4\text{-C}_{14}$ heteroarylalkyl; wherein said hydrocarbyl group is substituted with at least two hydroxyl groups, and is optionally substituted with oxo, acyl, alkoxy, alkoxy carbonyl, alkyl, alkenyl, alkynyl, amino, amido, azido, aryl, heteroaryl, carboxylic acid, cyano, guanidino, halo, haloalkyl, haloalkoxy, hydrazino, ODMT, alkylsulfonyl, nitro, sulfide, disulfide, sulfone, sulfonate, sulfonamide, thiol, and thioalkoxy; provided that X_6 is not hydrogen and X_6' is not a bond;

R_1 is hydrogen or a hydroxyl protecting group;

R_4 is a hydroxyl group or a protected hydroxyl group;

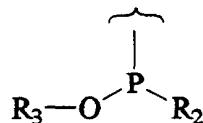
each R_5 and R_{40} is, independently, hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{20}$ alkynyl, $\text{C}_6\text{-C}_{14}$ aryl or an amino-protecting group

R_{50} is hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{20}$ alkynyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_6\text{-C}_{14}$ aralkyl, $\text{C}_3\text{-C}_{14}$ cycloalkyl, formyl,

aminoalkyl or hydroxymethyl;

R₆ is hydrogen or an amino protecting group;

R₂₀ is hydrogen or a group of formula:



5 R₂ is -N(R₇)₂, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

10 R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

R₂₁ is hydrogen, hydroxyl, fluoro or a group of formula Z-R₂₂-(R₂₃)_v;

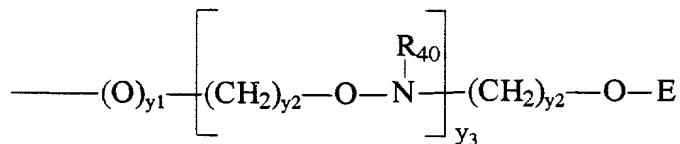
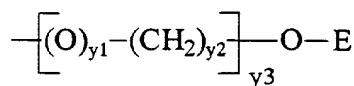
Z is O, S, NH or N-R₂₂-(R₂₃)_v;

15 R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl,

20 amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the 25 pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

or R₂₁ has one of the formulas:



wherein:

y₁ is 0 or 1;

each y₂ is, independently, 0 to 10;

5 y₃ is 1 to 10;

E is N(R₄₁)(R₄₂) or N=C(R₄₁)(R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken together with 10 the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

B is a nucleobase;

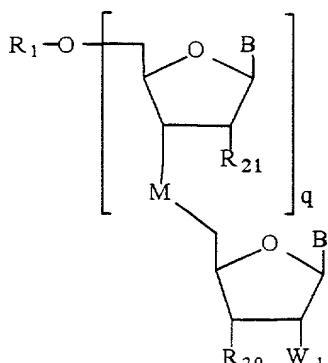
M is an optionally protected internucleoside linkage;

15 q is from zero to about 50; and

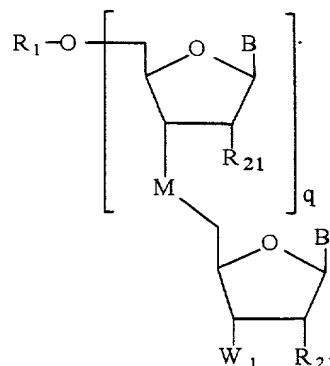
v is from zero to about 10.

23. A synthetic method comprising the steps of:

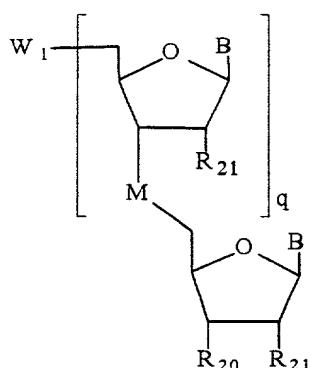
(a) providing a compound of formula IA, IB, IC or ID:



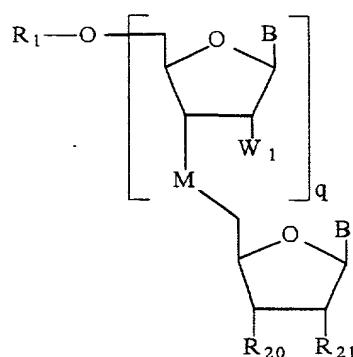
IA



IB



IC



ID

wherein:

W₁ is a linking group, O, NH, or S;

R₁ is H or a hydroxyl protecting group;

5 B is a nucleobase;

each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

Z is O, S, NH, or N-R₂₂-(R₂₃)_v

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

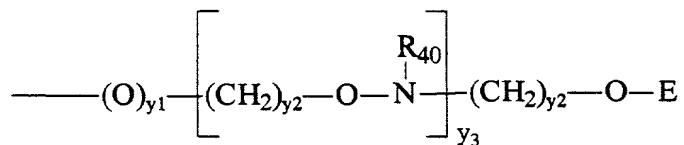
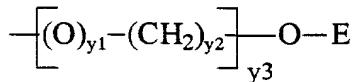
R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol,

10 keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, 15 disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide,

polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

5 v is from 0 to about 10;

or R_{21} has one of the formulas:



wherein:

10 y1 is 0 or 1;

y2 is 0 to 10;

y3 is 1 to 10;

E is $\text{N}(\text{R}_{41})$ (R_{42}) or $\text{N}=\text{C}(\text{R}_{41})$ (R_{42});

each R_{41} and each R_{42} is independently H, C_1-C_{10}

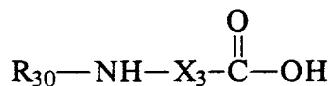
alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken

15 together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

q is from 0 to about 50;

20 M is an optionally protected internucleoside linkage;

(b) reacting said compound of formula I with a compound of formula II:



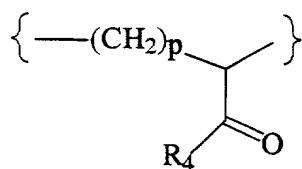
II

wherein:

R₃₀ is an amino protecting group;

X₃ is -CH(Z₁)- or a group of Formula XI:

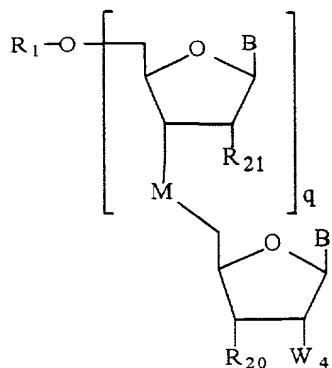
5



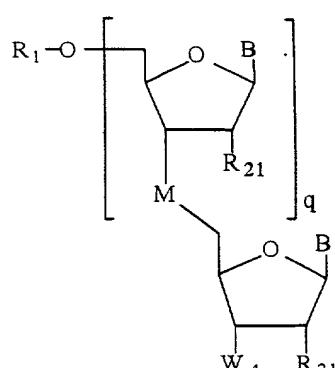
XI

Z₁ is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;
p is 1 or 2;

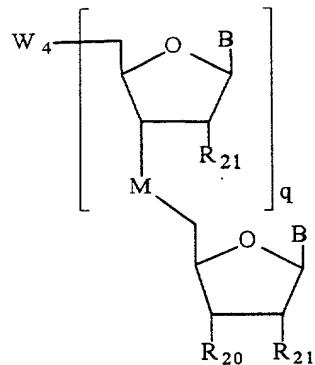
10 to form a compound of formula IVA, IVB, IVC, or IVD:



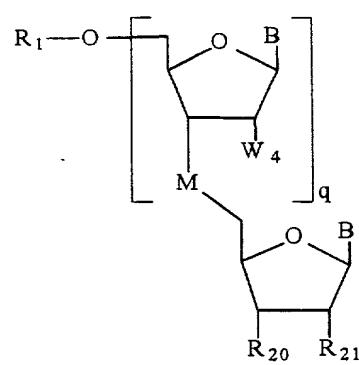
IV A



IV B



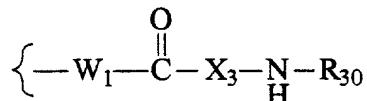
IV C



IV D

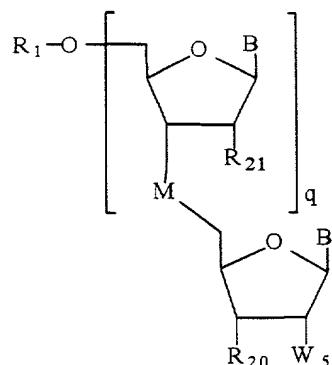
wherein:

W_4 has the formula:

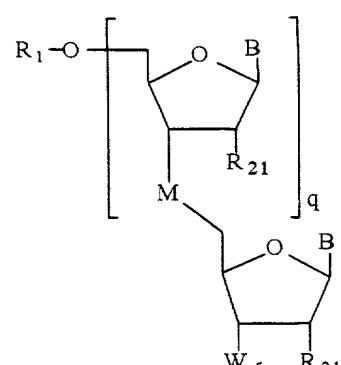


5 and

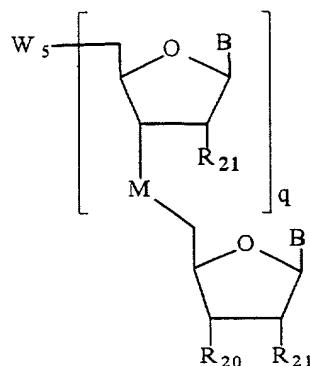
treating said compound of formula IVA, IVB, IVC or IVD with a deprotecting reagent to form a compound of formula VA, VB, VC or VD:



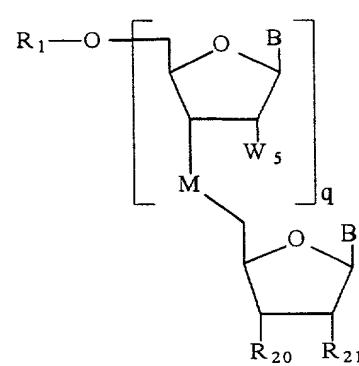
VA



VB

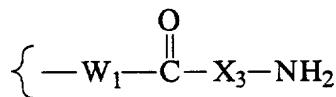


VC

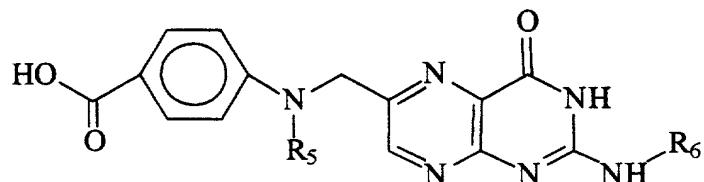


VD

wherein W_5 has the formula:



24. The method of claim 23 further comprising
 5 condensing said compound of formula V with a compound of
 formula VI:

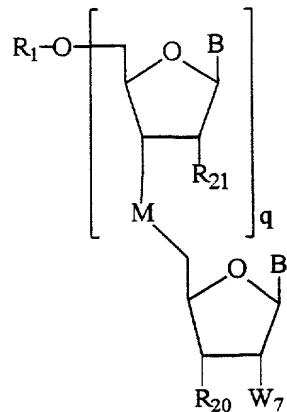


VI

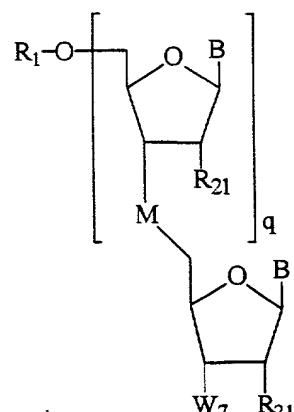
R₅ is H or an amino protecting group;

R₆ is H or an amino protecting group;

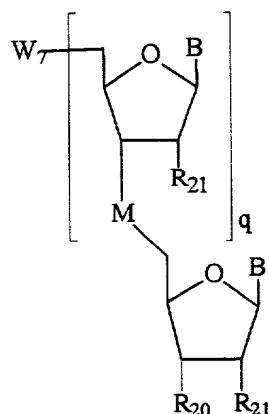
to form a compound of formula VIIA, VIIB, VIIC, or VIID:



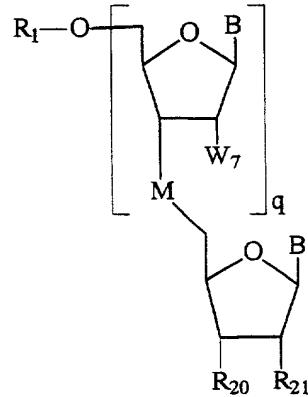
VIIA



VIIIB

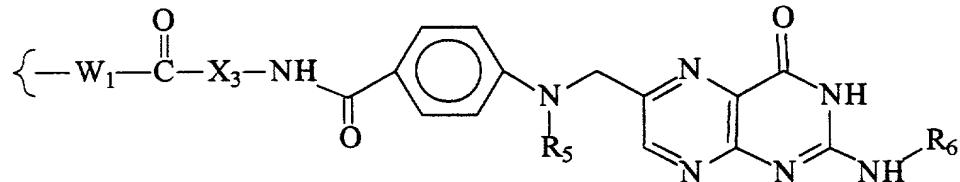


VIIC

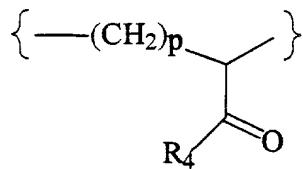


VIID

5 wherein W₇ has the formula:



25. The method of claim 24 wherein X_3 is a group of formula XI:

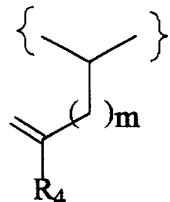


XI

5 wherein:

p is 1 or 2;

R_4 is a hydroxyl group, or a protected hydroxy group; or X_3 is a group of formula XII:



XII

10

wherein m is 1 or 2.

26. The method of claim 25 wherein q is 0.

27. The method of claim 25 wherein R_{30} is fluorene-9-yl methoxycarbonyl.

15 28. The method of claim 25 wherein X_3 is a group of formula XI.

29. The method of claim 25 wherein W_1 has the formula $-O-(CH_2)_n-NH-$, wherein n is from 1 to about 10.

30. The method of claim 29 wherein n is 6.

20 31. The method of claim 25 wherein X_3 is a group of formula XII.

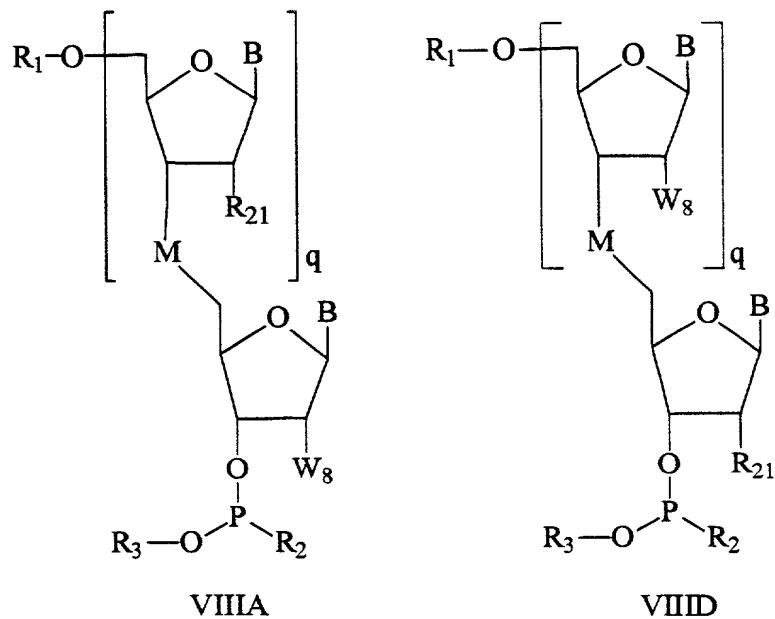
32. The method of claim 31 wherein W_1 has the formula $-O-(CH_2)_n-NH-$, wherein n is from 1 to about 10.

33. The method of claim 32 wherein n is 6.

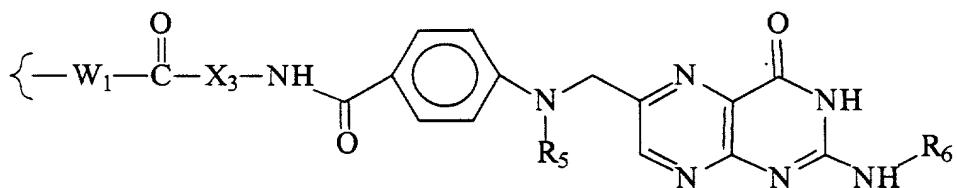
34. The method of claim 28 wherein R_1 is
5 dimethoxytrityl, W_1 has the formula $-O-(CH_2)_n-NH-$ where n is
6, p is 2, R_4 is *t*-butoxy, R_5 is trifluoroacetyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

35. The method of claim 31 wherein R_1 is dimethoxytrityl, A has the formula $-O-(CH_2)_n-NH-$ where n is 6, 10 m is 2, R_4 is t-butoxy, R_5 is trifluoroacetyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

36. The method of claim 24 further comprising
contacting said compound of formula VIIA or VIID with a
phosphitylating reagent to form a compound of formula VIIIA
15 or VIIID:



wherein W_7 has the formula:



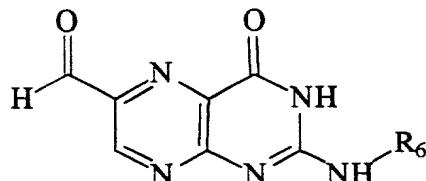
37. The method of claim 36 wherein X_3 has the formula XI.

5 38. The method of claim 36 wherein X_3 has the formula XII.

39. The method of claim 37 wherein R_1 is dimethoxytrityl, W_1 has the formula $-O-(CH_2)_n-NH-$ where n is 6, p is 2, R_4 is t-butoxy, R_5 is trifluoroacetyl, R_6 is $-10\ C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

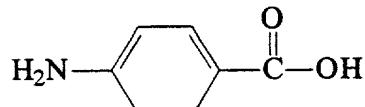
40. The method of claim 38 wherein R_1 is dimethoxytrityl, W_1 has the formula $-O-(CH_2)_n-NH-$ where n is 6, m is 2, R_4 is t-butoxy, R_5 is trifluoroacetyl, R_6 is $-C(=O)-CH(CH_3)_2$, and R_{30} is FMOC.

15 41. The method of claim 25 wherein said compound of formula VI is prepared by the steps of reacting a compound of formula IX:



IX

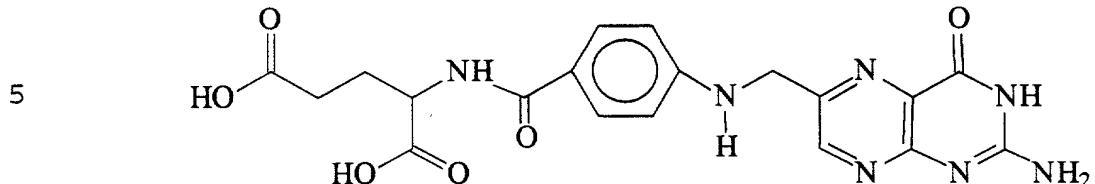
20 with a compound of formula X:



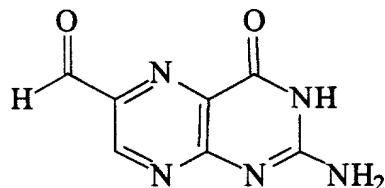
X

and treating the product of said reaction with a protecting group reagent to form said compound of formula VI.

42. The method of claim 26 wherein said compound IX is prepared by reacting folic acid:



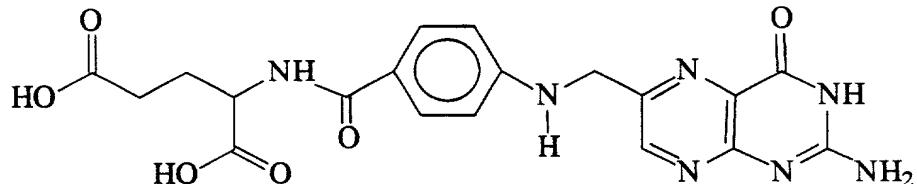
with a reagent effective to form pterin aldehyde:



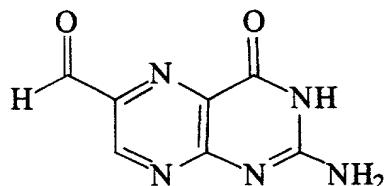
and

protecting the amino group of said pterin aldehyde.

10 43. A method for the preparation of a folic acid derivative comprising the steps of reacting folic acid:

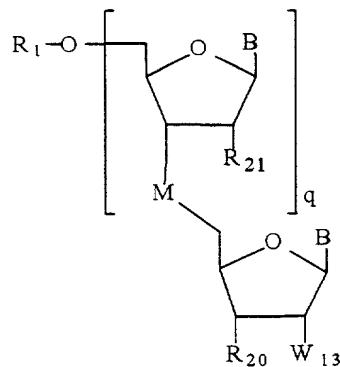


with a reagent effective to form pterin aldehyde:

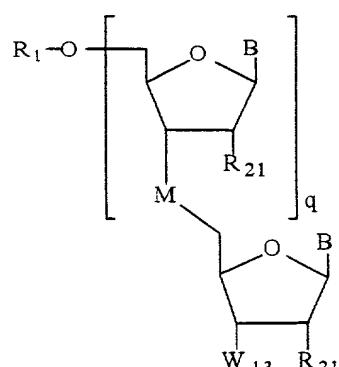


15 44. The method of claim 43 further comprising protecting the amino group of said pterin aldehyde.

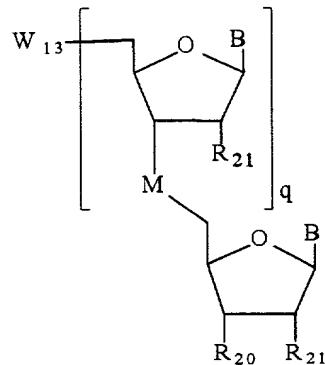
45. A compound having the formula XIII A, XIII B, XIII C or XIII D:



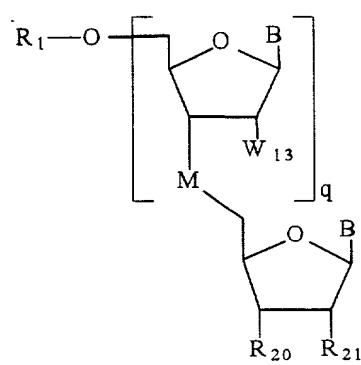
XIII A



XIII B



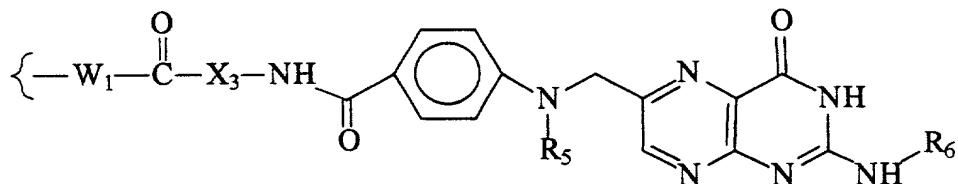
XIII C



XIII D

wherein:

5 W_{13} has the formula:



10 R_1 is H or a hydroxyl protecting group;

 B is a nucleobase;

 each R_{21} is H, OH, F, or a group of formula $Z-R_{22}-(R_{23})_v$;

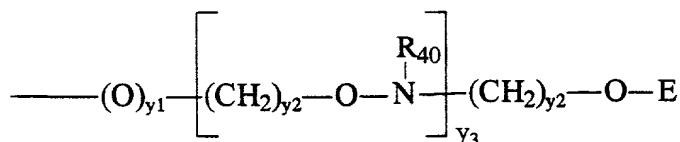
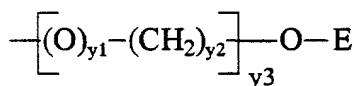
 Z is O, S, NH or $N-R_{22}-(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol,

keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino,
 5 hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group
 10 that enhances the pharmacokinetic properties of oligonucleotides;

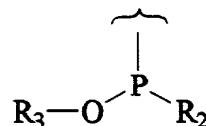
or R_{21} has one of the formulas:



wherein:

15 y_1 is 0 or 1;
 y_2 is 0 to 10;
 y_3 is 1 to 10;
 E is $\text{N}(\text{R}_{41})(\text{R}_{42})$ or $\text{N}=\text{C}(\text{R}_{41})(\text{R}_{42})$;
 each R_{41} and each R_{42} is independently H, $\text{C}_1\text{--C}_{10}$
 20 alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;
 25 v is from 0 to about 10;
 q is from 0 to about 50;
 M is an optionally protected internucleoside linkage;
 W_1 is a linking group, O, NH or S;

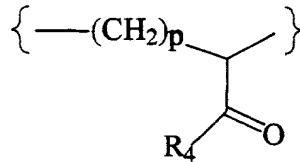
R₂₀ is H or a group of Formula:



R₂ is -N(R₇)₂, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and 5 having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;
 10 n is from 1 to about 10;
 R₅ is H or an amino protecting group;
 R₆ is H or an amino protecting group;
 X₃ is -CH(Z₁)- or a group of Formula XI:



15 XI

Z₁ is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

20 p is 1 or 2; and
 R₄ is a hydroxyl group, or a protected hydroxy group.

46. The compound of claim 45 wherein W₁ is -O-(CH₂)_n-NH- where n is from 1 to about 10.

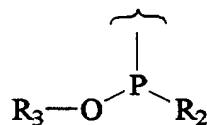
47. The compound of claim 45 wherein n is 6.

48. The compound of claim 45 wherein R₁ is

dimethoxytrityl, R₅ is trifluoroacetyl, and R₆ is -C(=O)-CH(CH₃)₂, and R₄ is t-butoxy.

49. The compound of claim 45 wherein q is 0.

50. The compound of claim 45 wherein R₂₀ is a group of
5 formula:



wherein R₃ is β-cyanoethyl, and R₂ is diisopropylamino.

51. The compound of claim 50 wherein W₁ is
-O-(CH₂)₆-NH-, R₁ is dimethoxytrityl, R₅ is
10 trifluoroacetyl, R₆ is -C(=O)-CH(CH₃)₂, and R₄ is t-butoxy.

52. The compound of claim 50 wherein q is 0.

53. The compound of claim 45 wherein X₃ has the formula
XI.

54. The compound of claim 53 wherein p is 2.

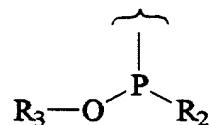
15 55. The compound of claim 54 wherein W₁ is
-O-(CH₂)₆-NH-.

56. The compound of claim 55 wherein R₄ is t-butoxy.

57. The compound of claim 56 wherein R₁ is
dimethoxytrityl, R₅ is trifluoroacetyl, and R₆ is
20 -C(=O)-CH(CH₃)₂.

58. The compound of claim 57 wherein q is 0.

59. The compound of claim 58 wherein R_{20} is a group of formula:

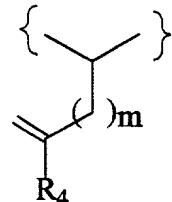


wherein R_3 is β -cyanoethyl, and R_2 is diisopropylamino.

5 60. The compound of claim 57 wherein R_{20} is H.

61. The compound of claim 60 wherein q is 0.

62. The compound of claim 45 wherein X_3 has the formula
XII:



10

XII

wherein m is 1 or 2.

63. The compound of claim 62 wherein m is 2.

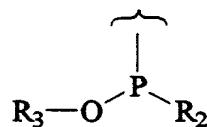
64. The compound of claim 63 wherein W_1 is
 $-O-(CH_2)_6-NH-$.

15 65. The compound of claim 54 wherein R_4 is t-butoxy.

66. The compound of claim 65 wherein R_1 is dimethoxytrityl, R_5 is trifluoroacetyl, and R_6 is $-C(=O)-CH(CH_3)_2$.

67. The compound of claim 66 wherein q is 0.

68. The compound of claim 67 wherein R_{20} is a group of formula:

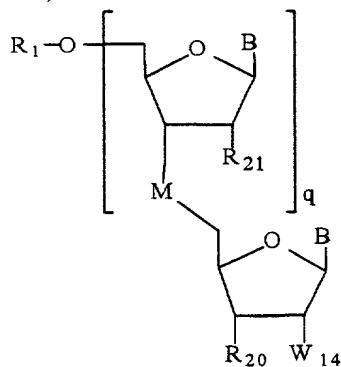


where R_3 is β -cyanoethyl, and R_2 is diisopropylamino.

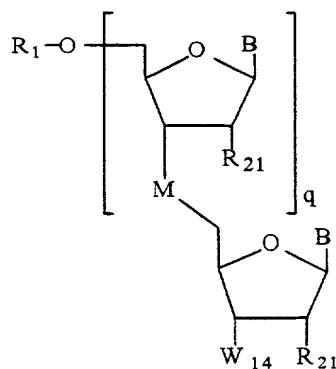
5 69. The compound of claim 45 wherein R_{20} is H.

70. The compound of claim 69 wherein q is 0.

71. A composition comprising a compound of claim 54, said composition being substantially free of a compound of formula XIVA, XIVB, XIVC, or XIVD:

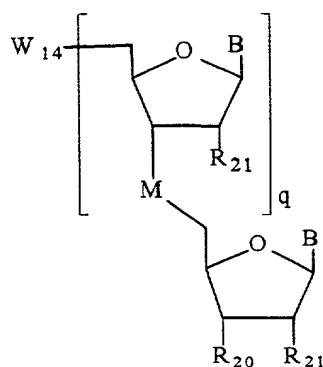


XIVA

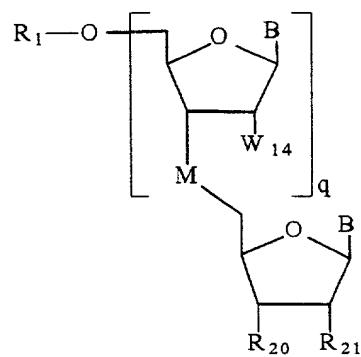


XIVB

10



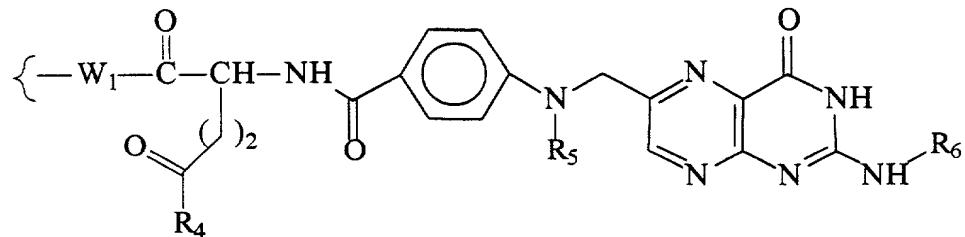
XIVC



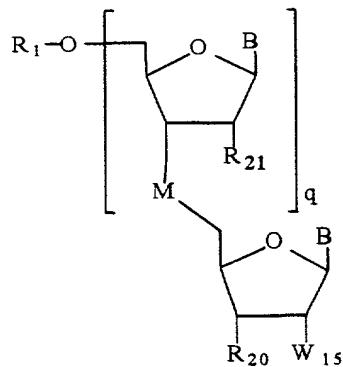
XIVD

wherein:

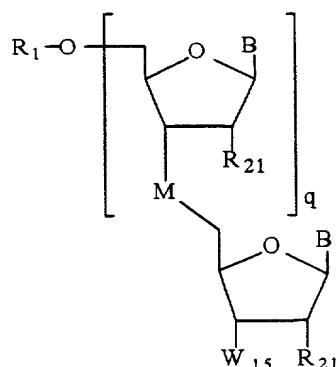
W_{14} has the formula:



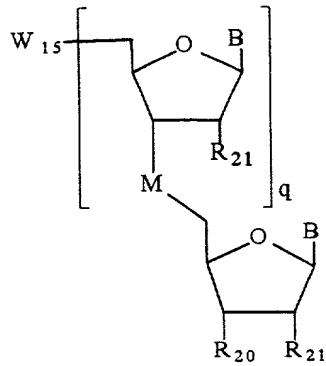
72. A composition comprising a compound of claim 63,
5 said composition being substantially free of a compound of
formula XVA, XVB, XVC or XVD:



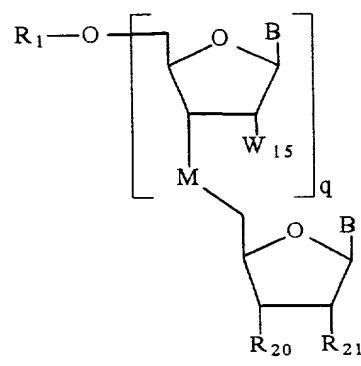
XVA



XVB

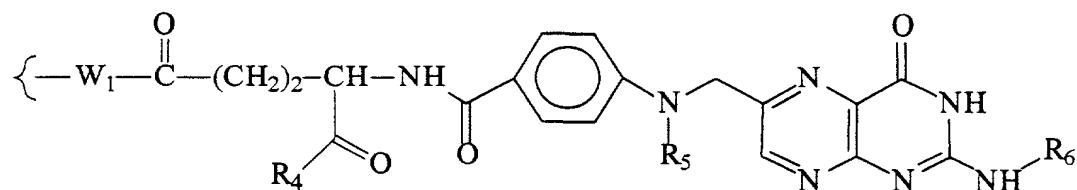


XVC

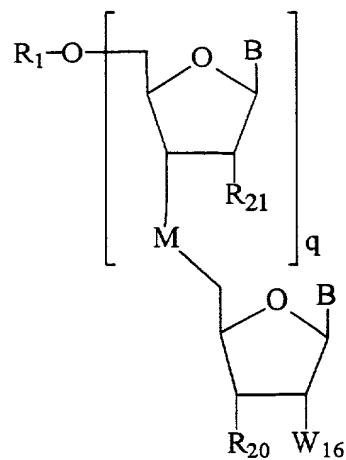


XVD

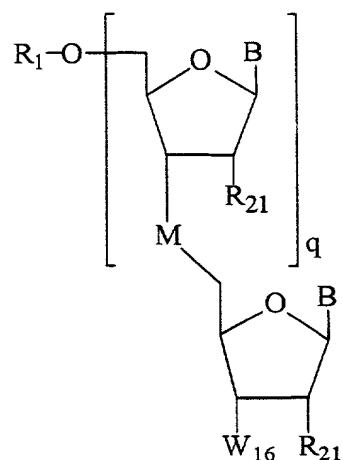
wherein W_{15} has the formula:



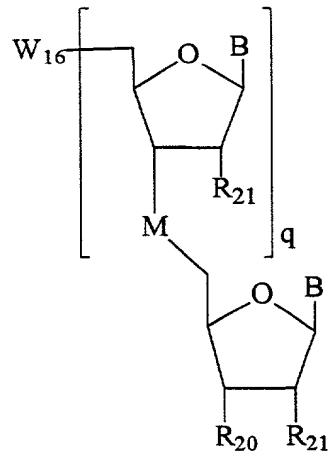
73. A compound having the formula XVIA, XVIB, XVIC or XVID:



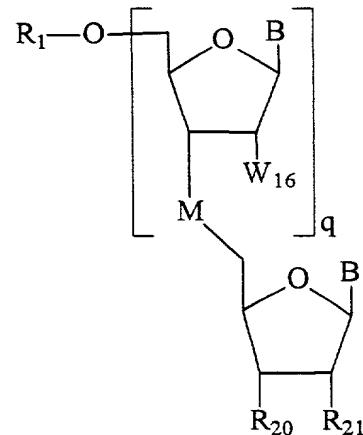
XVIA



XVIB



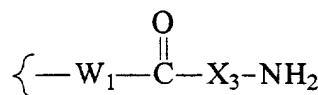
XVIC



XVID

5 wherein:

W₁₆ has the formula:



R₁ is H or a hydroxyl protecting group;

B is a nucleobase;

each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

5 Z is O, S, NH or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₁-C₂₀ alkoxy, C₂-C₂₀ alkenyloxy, or C₂-C₂₀ alkynyloxy;

10 R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl,

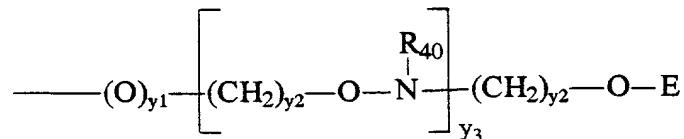
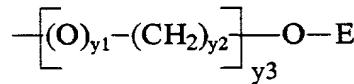
trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl,

amino, N-phthalimido, imidazole, azido, hydrazino,

hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, inter-

15 calator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

20 or R₂₁ has one of the formulas:



wherein:

y₁ is 0 or 1;

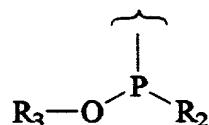
y₂ is 0 to 10;

25 y₃ is 1 to 10;

E is $N(R_{41})(R_{42})$ or $N=C(R_{41})(R_{42})$;
each R_{41} and each R_{42} is independently H, C_1-C_{10} alkyl, a nitrogen protecting group, or R_{41} and R_{42} taken together form a nitrogen protecting group; or R_{41} and R_{42} taken together with the N or C atom to which they are attached form a ring structure that can include at least one heteroatom selected from N and O;

v is from 0 to about 10;
q is from 0 to about 50;

M is an optionally protected internucleoside linkage;
 W_1 is a linking group;
 R_{20} is H or a group of Formula:



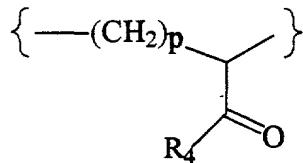
15 R_2 is $-N(R_7)_2$, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

20 R_7 is straight or branched chain alkyl having from 1 to 10 carbons;

20 R_3 is a phosphorus protecting group;

20 n is from 1 to about 10;

20 X_3 is $-CH(Z_1)-$ or a group of Formula XI:



xi

25 Z₁ is the sidechain of a naturally occurring amino acid,
or a protected sidechain of a naturally occurring amino acid;
and

p is 1 or 2.

74. The compound of claim 73 wherein X_3 has the formula XI.

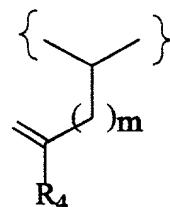
75. The compound of claim 74 wherein p is 2.

5 76. The compound of claim 75 wherein W_1 is $-O-(CH_2)_n-NH-$ wherein n is from 1 to about 10.

77. The compound of claim 76 wherein n is 6.

78. The compound of claim 73 wherein X_3 has the formula XII:

10



XII

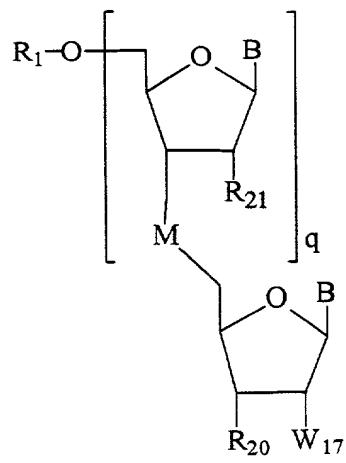
wherein m is 1 or 2.

79. The compound of claim 78 wherein m is 2.

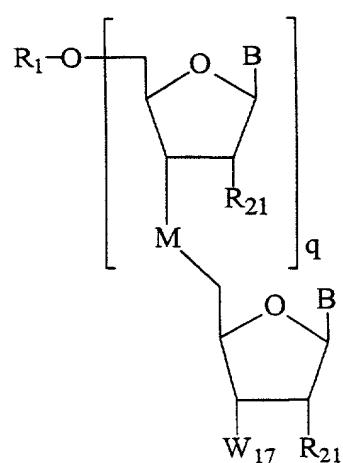
80. The compound of claim 79 wherein W_1 is $-O-(CH_2)_n-NH-$ 15 wherein n is from 1 to about 10.

81. The compound of claim 80 wherein n is 6.

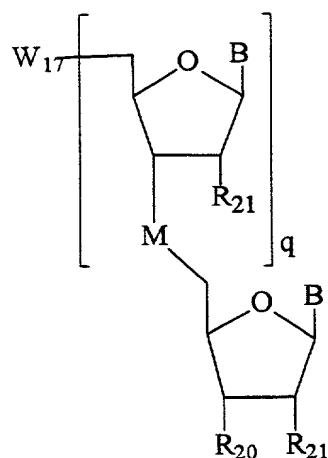
82. A compound having the formula XVIIA, XVIIB, XVIIC or XVIID:



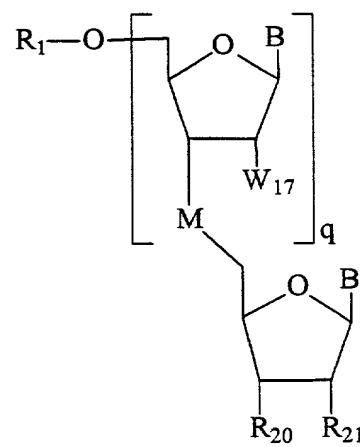
XVIIA



XVIIIB



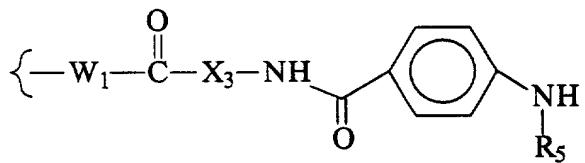
XVIIIC



XVIID

wherein:

W₁₇ has the formula:



5 R₁ is H or a hydroxyl protecting group;
 B is a nucleobase;
 each R₂₁ is H, OH, F, or a group of formula Z-R₂₂-(R₂₃)_v;

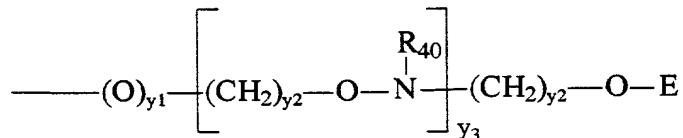
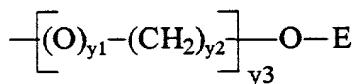
Z is O, S, NH or N-R₂₂-(R₂₃)_v;

R₂₂ is C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, or C₂-C₂₀ alkynyl;

R₂₃ is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl,

5 trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, inter-
10 calator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

15 or R₂₁ has one of the formulas:



wherein:

y₁ is 0 or 1;

y₂ is 0 to 10;

20 y₃ is 1 to 10;

E is N(R₄₁) (R₄₂) or N=C(R₄₁) (R₄₂);

each R₄₁ and each R₄₂ is independently H, C₁-C₁₀ alkyl, a nitrogen protecting group, or R₄₁ and R₄₂ taken together form a nitrogen protecting group; or R₄₁ and R₄₂ taken 25 together with the N or C atom to which they are attached form a ring structure that can include at least one heterotom selected from N and O;

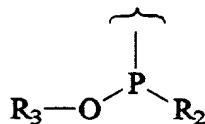
v is from 0 to about 10;

q is from 0 to about 50;

M is an optionally protected internucleoside linkage;

W₁ is a linking group, O, NH or S;

R₂₀ is H or a group of formula:



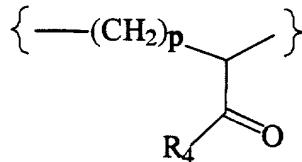
5 R₂ is -N(R₇)₂, or a heterocycloalkyl or heterocycloalkenyl ring containing from 4 to 7 atoms, and having up to 3 heteroatoms selected from nitrogen, sulfur, and oxygen;

10 R₇ is straight or branched chain alkyl having from 1 to 10 carbons;

R₃ is a phosphorus protecting group;

n is from 1 to about 10;

X₃ is -CH(Z₁)- or a group of formula XI:



15

XI

Z₁ is the sidechain of a naturally occurring amino acid, or a protected sidechain of a naturally occurring amino acid;

p is 1 or 2; and

R₅ is H or an amino protecting group.

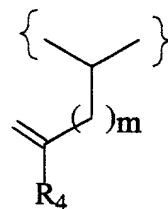
20 83. The compound of claim 82 wherein X₃ has the formula XI.

84. The compound of claim 83 wherein p is 2.

85. The compound of claim 84 wherein W₁ is -O-(CH₂)_n-NH- wherein n is from 1 to about 10.

86. The compound of claim 85 wherein n is 6.

87. The compound of claim 82 wherein X_3 has the formula XII:



5

XII

wherein m is 1 or 2.

10

90. The compound of claim 89 wherein n is 6.

91. A folate conjugate comprising a folate moiety covalently linked to an amino acid, said amino acid further connected to a hydrocarbyl group, said hydrocarbyl group bearing at least two hydroxyl groups.

15

92. An oligonucleotide-folate conjugate comprising a folate moiety covalently linked to an amino acid, said amino acid being connected to a hydrocarbyl group, said hydrocarbyl group further connected to an oligonucleotide, said hydrocarbyl group bearing at least two hydroxyl groups.

20

93. The compound of claim 7 wherein said R₄ is a hydroxyl group protected with C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl or C₂-C₂₀ alkynyl.

94. The compound of claim 13 wherein said R₄ is a

hydroxyl group protected with C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl or C₂-C₂₀ alkynyl.

95. The compound of claim 16 wherein said R₄ is a hydroxyl group protected with C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl or 5 C₂-C₂₀ alkynyl.

96. The method of claim 19 wherein said R₄ is a hydroxyl group protected with C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl or C₂-C₂₀ alkynyl;

10 further comprising the step of deprotecting said R₄ with a deprotecting reagent.

97. The method of claim 96 wherein said deprotecting reagent is an aqueous amine.

98. The method of claim 97 wherein said amine is piperidine, pyrrolidine, piperazine or morpholine.

15 99. The method of claim 96 wherein said deprotecting reagent comprises an aqueous amine and a mercapto compound.

100. The method of claim 99 wherein the concentration of said mercapto compound is 2-10%.